Early versus late dialysis in AKI

By
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Incidence of AKI is continuing to rise

RECOGNISE · RESUSCITATE · REFER

S. S. Waikar et al.(2008).*ClinicalJournal of theAmerican Society of Nephrology, vol. 3, no. 3*


Renal
replacement
therapy


costs

Why early versus late dialysis still a debate?

- Definition of AKI.
- Heterogenous population
- Definition of the term early
- Definition of the term late
- Definition of indication
- Different modalities of dialysis
- Definition of outcome

Definition of AKI

- Absolute increases in creatinine.
- Relative increase from baseline.

(R. Bellomo, et *Critical Care, vol. 8, no. 4, pp. R204–R212, 2004)*.

- Requirement for RRT .

(R. L. Mehta, et al., *Critical Care, vol. 11, no. 2, article* R31, 2007).

2004

A consensus on the definition of acute renal failure known as (RIFLE) classification was reached by a group of international experts .The RIFLE classification was based on two important parameters: (1) changes in serum creatinine or GFR from baseline (2) urine output at specific time points. The severity was determined by the more severe of the two parameters]

2007

The RIFLE classification was modified by the Acute Kidney Injury Network (AKIN)

RRT: renal replacement therapy.

[1]Patients requiring RRT are automatically considered stage 3 AKIN regardless of stage at time of RRT initiation.

AKIN classification

(1) Recategorisation of the original RIFLE into AKIN stage 1, 2, and 3.

(2) Addition of an absolute increase in creatinine *≥26 µmol/L (0.3mg/dL)* to stage 1 *criteria.*

(3) Automatic classification of patients starting RRT as stage 3, regardless of creatinine or urine output .

(R. L. Mehta, et al., *Critical Care, vol. 11, no. 2, article* R31, 2007).

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Timing of RRT

A major barrier towards determining the optimal timing for RRT initiation has been the lack of agreement over the absolute indications for RRT.

Initiating RRT

Non Critical

High Severity
Low Priority

Severity

Critical

High Severity
High Priority

In the noncritical care patient with AKI,RRT is regarded as a supportive therapy. Traditional indications have been based on criteria used for ESRD patients .

P. M. Palevsky, "Indications and timing of renal replacement therapy in acute kidney injury," *Critical Care Medicine, vol.* 36, no. 4, pp. S224–S228, 2008.

Traditional indications for RRT

- Volume overload unresponsive to diuretics
- Metabolic acidosis refractory to medical management
- Intoxication with dialyzable drug or toxin
- Uremic complications
  - Encephalopathy
  - Pericarditis
  - Uremic bleeding
- Progressive azotemia in the absence of specific symptoms

Indications are open to interpretations

- **How** volume overloaded?
- **What** is the definition of diuretic resistance?
- **What** should potassium level be?
- **How** severe for metabolic acidosis?

Recommended relative and absolute indications for RRT in critically ill patients with AKI

Dialysis indication	Criteria	Absolute/relative
Metabolic	Urea > 27 mmol/L	Relative
	Urea > 35.7 mmol/L	Absolute
	Hyperkalaemia > 6 mmol/L	Relative
	Hyperkalaemia > 6 mmol/L plus ECG changes	Absolute
	Dysnatraemia	Relative
	Hypermagnesaemia > 4 mmol/L	Relative
	Hypermagnesaemia > 4 mmol/L plus anuria or areflexia	Absolute
Acidosis	pH > 7.15	Relative
	pH < 7.15	Absolute
Anuria/oliguria	Risk (RIFLE class)	Relative
	Injury (RIFLE class)	Relative
	Failure (RIFLE class)	Relative
	UO < 200 mL for 12 hrs or anuria	Absolute
Uraemic complication	Encephalopathy	Absolute
	Pericarditis	Absolute
	Myopathy	Absolute
	Neuropathy	Absolute
	Bleeding	Absolute
Fluid overload	Diuretic responsive	Relative
	Diuretic resistant (with pulmonary oedema)	Absolute

Gibney, et al., *Clinical Journal of the American Society of Nephrology, vol. 3, no. 3,2008*

Note certain situations

Specific “critical” conditions should be considered prior to determining whether to initiate RRT in patients with critical AKI.

clinical syndromes associated with high catabolic states such as septic shock, burns, or trauma or in other high “metabolic” scenarios such as gastrointestinal bleeding or rhabdomyolysis which often place a greater demand upon renal reserve .

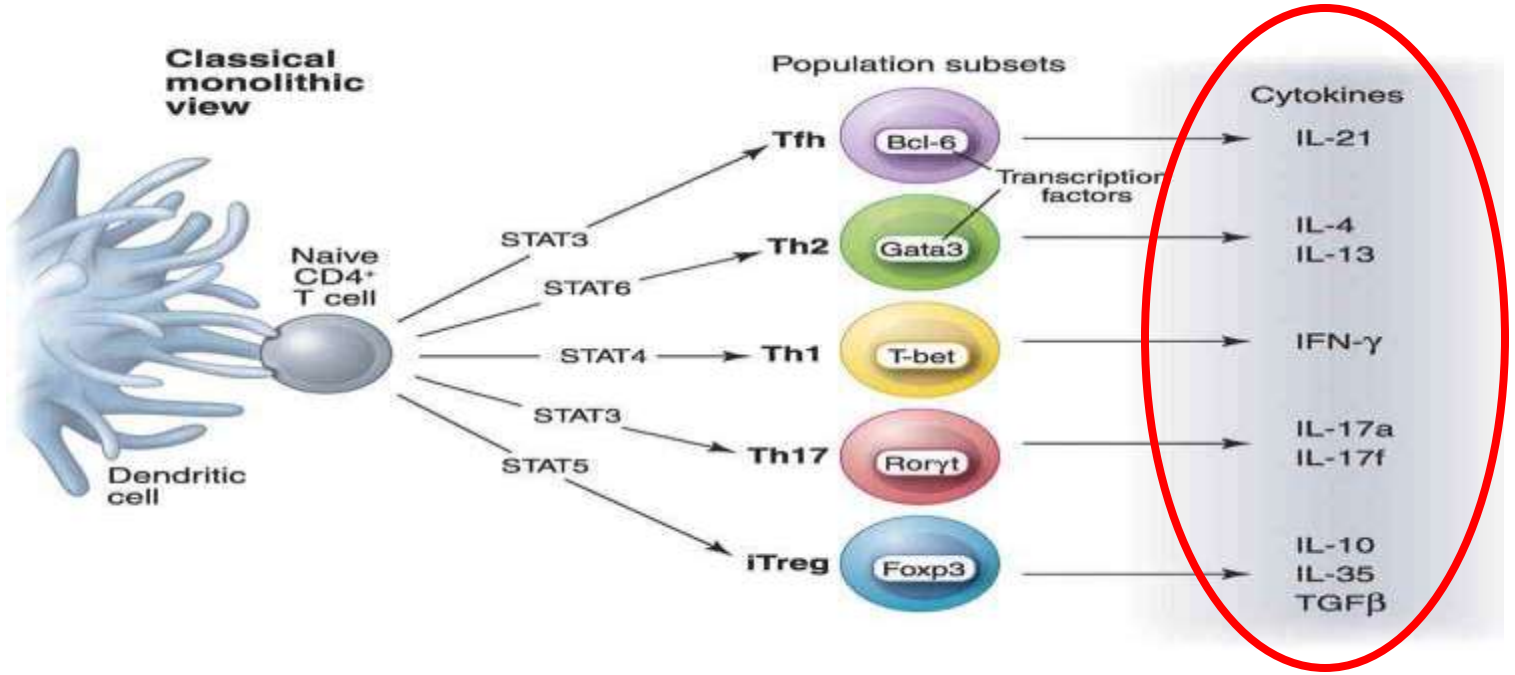
Cruz, Z, et al “Renal replacement therapy in adult critically ill patients: when to begin and when to stop,”, *vol. 165, pp. 263–273, 2010.*

fluid overload

- Studies demonstrating an association between positive fluid balance and worse outcomes in critically ill patients with AKI, sepsis, acute lung injury (ALI) and postsurgery.
- It has been hypothesised that fluid overload results in visceral oedema, which in turn promotes intra-abdominal hypertension and renal interstitial oedema, both of which may perpetuate AKI .

Prowle, et al. *Nature Reviews Nephrology, vol. 6, no. 2, 2010*

Growing data suggest an important role of the kidneys in the clearance of inflammatory molecules, which may be critical in the pathogenesis of ALI and acute respiratory distress syndrome (ARDS) as well as precipitating and/or exacerbating AKI.



Koyner and Murray, "Mechanical ventilation and the kidney," *Blood Purification, vol. 29, 2010.*

"criteria" for initiation of RRT based on hypercatabolic states, specific clinical states, fluid status and a pro-inflammatory state remain unclear.

These data may be seen to favour earlier initiation of RRT compared with traditional indicators for RRT.

Non modifiable factors play a role

- Age.
- Presence of comorbidities.
- Resource availability
- Cost
- Physician preference

Palevsky, “Indications and timing of renal replacement therapy in acute kidney injury,” *Critical Care Medicine, vol.* 36, no. 4, pp. S224–S228, 2008

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- The timing of RRT in patients with AKI was first assessed by Teschan et al. in 1960, who evaluated the effects of “prophylactic” haemodialysis in patients with oliguric AKI .
- In this **case series**, the mortality rate of patients with AKI in whom RRT was initiated prior to the urea reaching a level of 71.4mmol/L was 33%. This compared favourably with a reported mortality rate of 25–40% in historical controls.
- Subsequent Retrospective studies comparing early to late initiation of RRT have generally favoured early RRT

Teschan, C. R.et al. , *Annals of Internal Medicine, vol. 53, 1960*

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A CONTROLLED EVALUATION OF PROPHYLACTIC DIALYSIS IN POST-TRAUMATIC ACUTE RENAL FAILURE

JOHN D. CONGER, M.D.

From the Hemodialysis Unit, Veterans Administration Hospital, and Department of Medicine, University of Colorado Medical Center, Denver

INTRODUCTION

Evidence has been presented in the past several years that intensive dialysis is beneficial in improving the survival of patients with acute renal failure (6, 13, 14, 17, 21, 23, 25). However, all of these studies have a similar inherent defect: survival data before the advent of dialysis or in the relatively early years of dialysis are compared to those from more contemporary periods. It is possible that factors other than the frequency of dialysis, such as improved

related shutdown will likely have poorer survival results (4, 26) than reports in which there are a large number of medically related renal failure patients (5, 12).

We recently carried out a prospective study to evaluate specifically the value of dialysis treatment programs of differing intensities in the treatment of acute renal failure, designed to eliminate the aforementioned variables. Patients with similar degrees of trauma and catabolism with associated acute renal failure were

9 patient pairs (17 oligo-anuric) – 'Early' BUN 50mg/dl 20% Mortality
'Late' BUN 120mg/dl 64% Mortality

Conger et al conducted a study on US Naval Hospital Ship USS *Sanctuary* between April and October of 1970.18 patients with post-traumatic AKI Survival - 5/8 pts (64%) vs 2/10 (20%) pts. Major complications (Gram-neg. sepsis, hemorrhage) were less freq in intensive arm.

Increased Mortality in Early HD

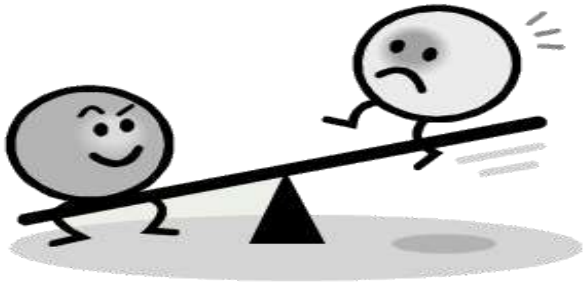
study	size	Design	Early criteria	Late criteria	Survival (early)	Survival (late)	P valu e
Parsons et al,1961	33	Retrospective	Urea: 45-56	Urea>75	75	12	N/A
Fischer et al,1966	162	Retrospective	Urea<56	Urea <75	43	26	N/A
Klienknecht et al,1972	500	Retrospective	Urea<35	Urea>61	73	58	<.05
Conger et al,1975	18	RCT	Urea<26 or Cr<442	Urea~56 or Cr~884 or clinically	64	20	NS
Gillum et al, 1986	34	RCT	Urea<22.5 +Cr<442	Urea~37. 5+Cr~795	41	53	NS
Getting et al,1989	100	Retrospective	BUN<60m g/dl	BUN>60m g/dl	39	20	N/A

study	size	design	Early	Late	Survival early	Survival late	P value
Bouman et al,2002	106	RCT	<12hrs after AKI diagnosis	K >6.5 or pul.oedema	69 (LV)to 74(HV)	75(LV)	
Demirkilic et al,2004	61	retrospective	UOP<100ml/ 8hr	Cr>442 or K>5.5	77	45	0.016
Elhai et al,2004	64	retrospective	UOP<100ml/ 8hr	Cr >250 or K>6	78	57	<.05
Piccini et al,2006	80	retrospective	<12hrs post ICU admission	Conventional	55	28	<.05
Liu et al,2006	243	prospective	Urea<28.5 or Cr<309	Urea>28.5 or Cr>309	65	59	.09
Bagshaw et al,2009	1238	prospective	Cr<309 or <2 days from ICU admission	Cr >309 or >5 days from ICU admission	(53-63)	(61-72)	<.001

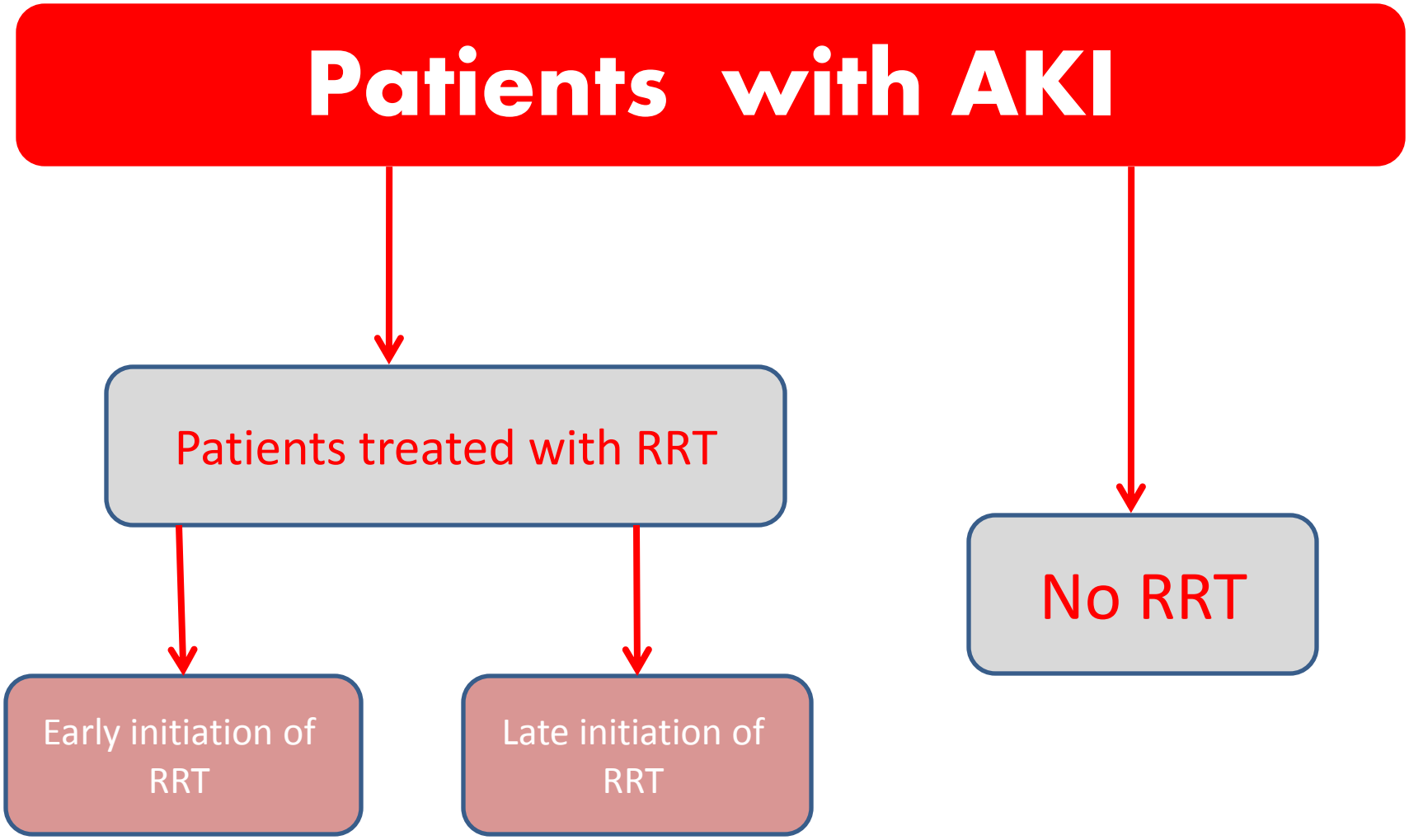
	TYPE OF STUDY	N	PARAMETER	EFFECT ES
Gettings et al, 1999	Retrospective	243	BUN 76	+
Guerin et al, 2000	Prospective Observational post hoc	510	Time after admission	0
Bouman et al, 2002	RCT*, 4 arms	106	Fixed time point (12 hrs) vs. classical parameters	0
Elahi et al, 2004	Retrospective	64	UO vs. other**	+
Demirkiliç et al, 2004	Retrospective	61	UO vs. other**	+
Liu et al, 2006	Observational	243	BUN 76	0 unadj + adj
Piccinni et al, 2006	Retrospective	80	Septic shock	+

Limitations of the studies

- All recent studies are retrospective
- Urea generation varies from patient to patient
- V_d of urea in critically ill patients is variable as well
- Using BUN as a surrogate measure of AKI duration is problematic
- Bias by indication



Design of observational studies



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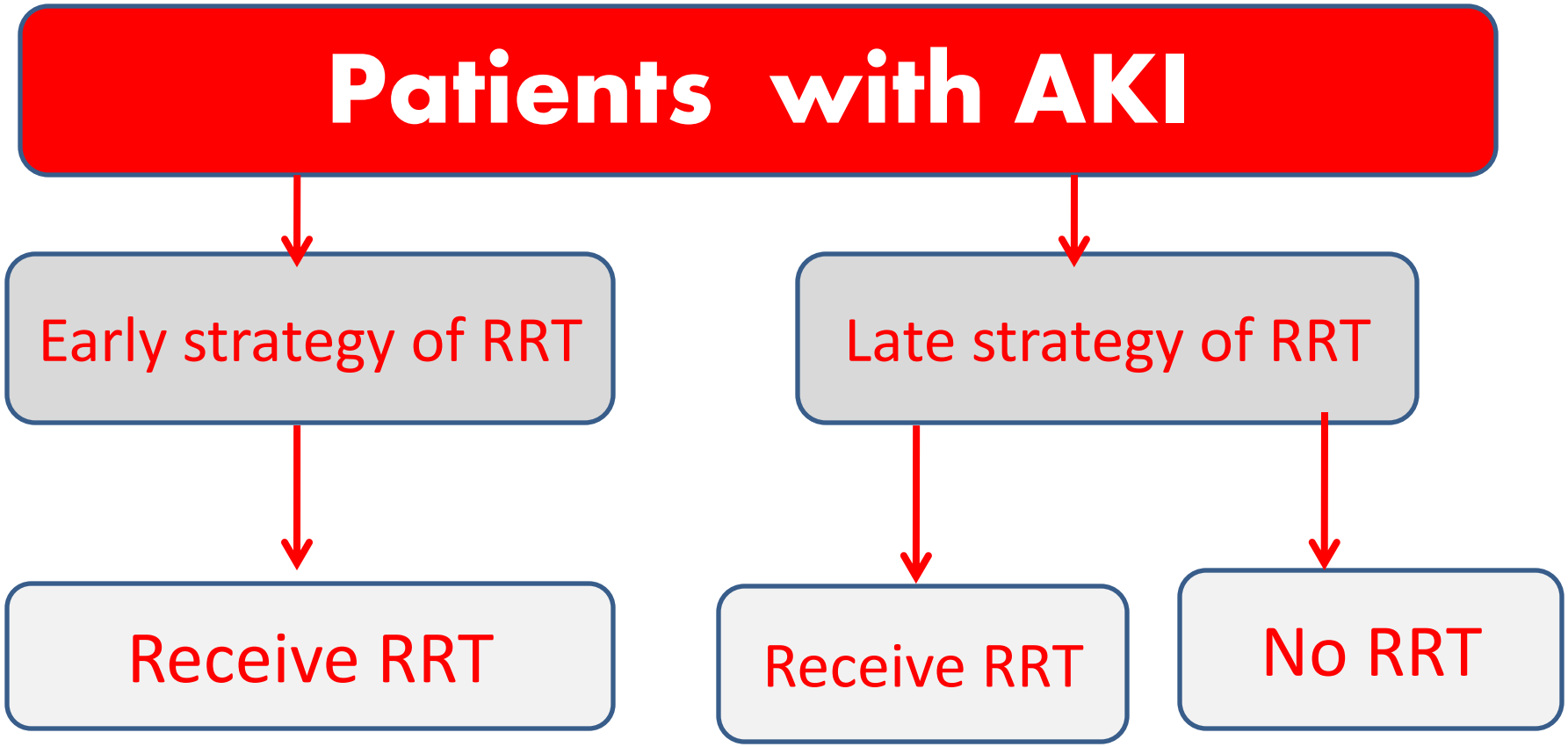
Trials. 2013; 14: 320.
Published online 2013 Oct 5. doi: 10.1186/1745-6215-14-320
PMCID: PMC3851593

Standard versus accelerated initiation of renal replacement therapy in acute kidney injury (STARRT-AKI): study protocol for a randomized controlled trial

Orla M Smith,[1,2] Ron Wald,[2,3,4] Neill KJ Adhikari,[5] Karen Pope,[6] Matthew A Weir,[7,8] and Sean M Bagshaw[✉9], on behalf of the Canadian Critical Care Trials Group

- This is an open-label pilot randomized controlled trial initiated may 2012.
- 100 critically ill patients with severe AKI will be randomly allocated 1:1 to receive "accelerated" initiation of RRT or "standard" initiation at 12 centers across Canada.
- In the accelerated arm, participants will have a venous catheter placed and renal replacement therapy will be initiated within 12 hours of fulfilling eligibility. In the standard initiation arm, participants will be monitored over 7 days to identify indications for renal replacement therapy.
- For participants in the standard arm with persistent acute kidney injury, the initiation of RRT will be discouraged unless one or more of the following criteria are fulfilled: serum potassium ≥6.0 mmol/L; serum bicarbonate ≤10 mmol/L; severe respiratory failure (PaO_2/FiO_2<200) or persisting acute kidney injury for ≥72 hours after fulfilling eligibility.

The required design to adequately answer timing of RRT in AKI



Inclusion Criteria (all of these need to be present):

- Age ≥ 18 years
- Admission to an intensive care unit
- Evidence of kidney dysfunction (serum creatinine ≥ 100 µmol/L (women) or ≥ 130 µmol/L (men))
- Evidence of severe AKI defined by at least 2 of the following 3 criteria:

  i-A 2-fold increase in serum creatinine during hospitalization or from a known pre-hospitalization baseline

  ii-Oliguria as defined by total urine output < 6 mL/kg over the preceding 12 hours

  iii-Whole blood Neutrophil Gelatinase-Associated Lipocalin (NGAL) ≥ 400ng/mL
- Likelihood that an absolute indication for RRT will not arise in the subsequent 24 hours based on the most recent bloodwork for the following parameters: i- Serum potassium ≤ 5.5 mmol/L and ii- Serum bicarbonate ≥ 15 mmol/L
- Central venous pressure ≥ 8 mmHg

The inclusion criteria are designed to identify a population of critically ill adults with severe AKI who are likely to need RRT during their hospitalization, but not immediately.).

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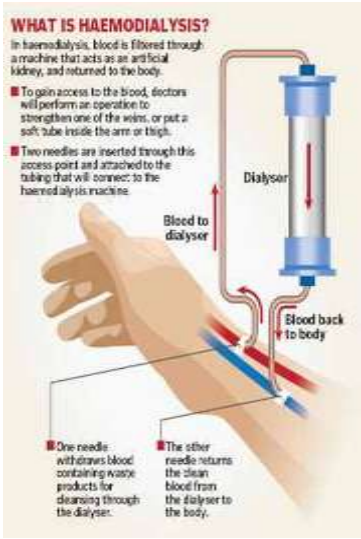
NDT Advance Access published October 14, 2008

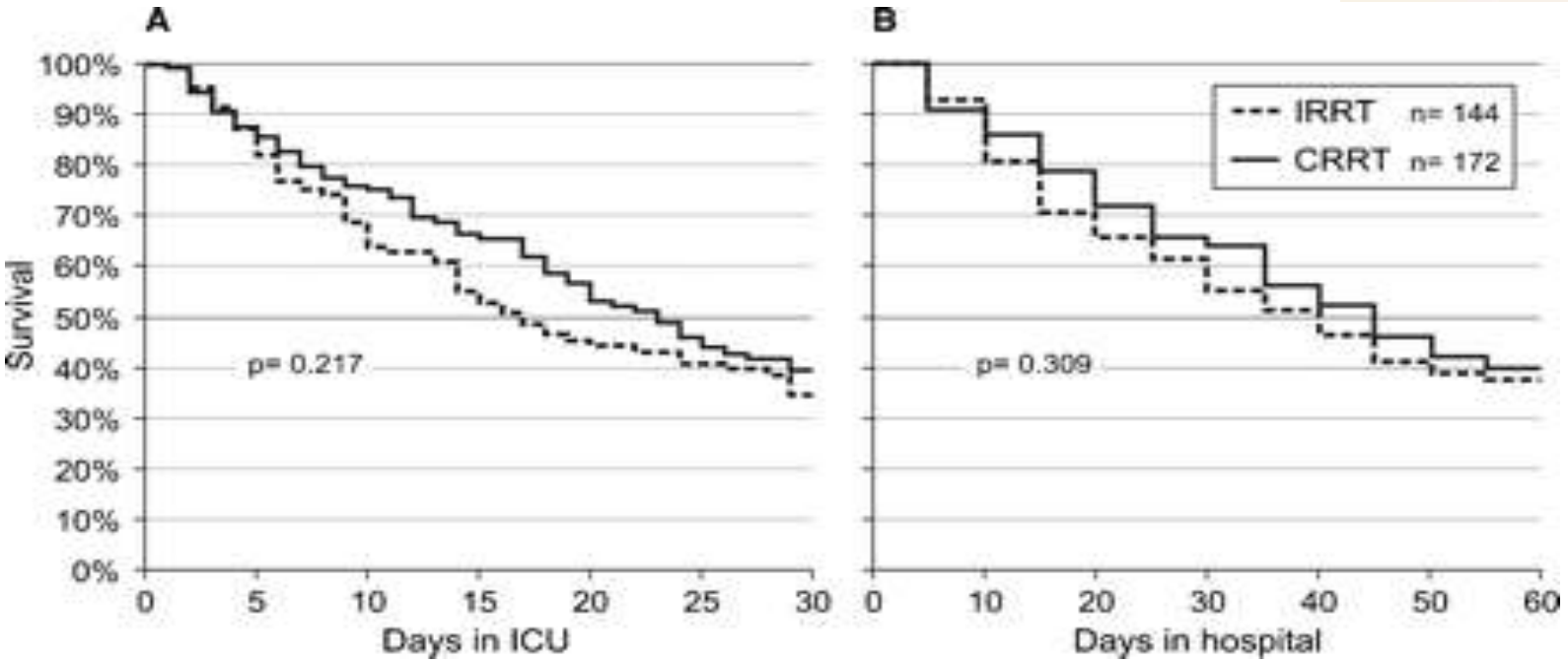
Nephrol Dial Transplant (2008) 1 of 7
doi: 10.1093/ndt/gfn560

NDT
Nephrology Dialysis Transplantation

Intermittent HD vs Continous Therapies



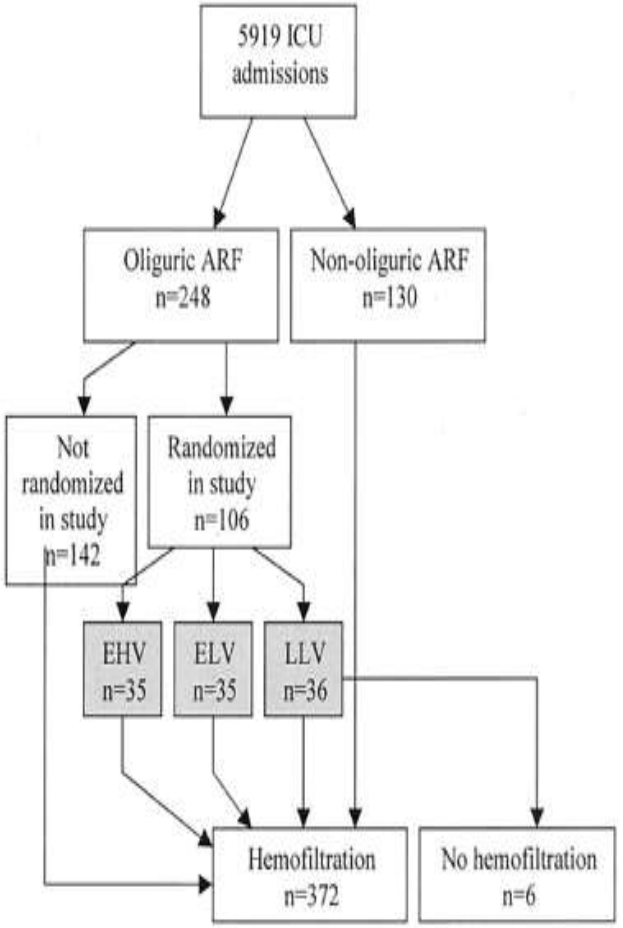
Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial



Lins et al, NDT, advance access published October 14, 2008

How about a prospective study of CRRT timing?

- Bouman et al randomized 106 criticall ill patients with AKI to three groups:
  - Early high-volume CVVHDF (35 pts)
  - Early low-volume CVVHDF (35 pts)
  - Late low-volume CVVHDF (36 pts)
- Two early groups – txt started within 12 hrs of meeting inclusion criteria:
  - **Oliguria x 6 hrs despite hemodynamic optimization**
  - **Measured cr clearance <20 ml/min on a 3-hr timed collection**
- Late groups:
  - **BUN>112**
  - **K>6.5**
  - **Pulmonary edema present**



are Med 2002 Vol. 30, No. 10 p. 2205

No significant differences in survival

Dose studies of AKI

- Hemodynamically unstable pts received CRRT or SLEDD, stable pts IRRT
- Intensive RRT= IRRT or SLEDD 6x/wk or CRRT at 35 ml/kg/hr
- Less intensive RRT= IRRT or SLEDD 3x/wk or CRRT at 20 ml/kg/hr

RENAL study

VA/NIH (ATN)

Don’t have too much of a good thing

- IRRT: 3x/week
- CRRT: delivered effluent flow rate of at least 20 mL/kg/hr

Up To Date.com

Why early versus late dialysis still a debate?

- Definition of AKI.
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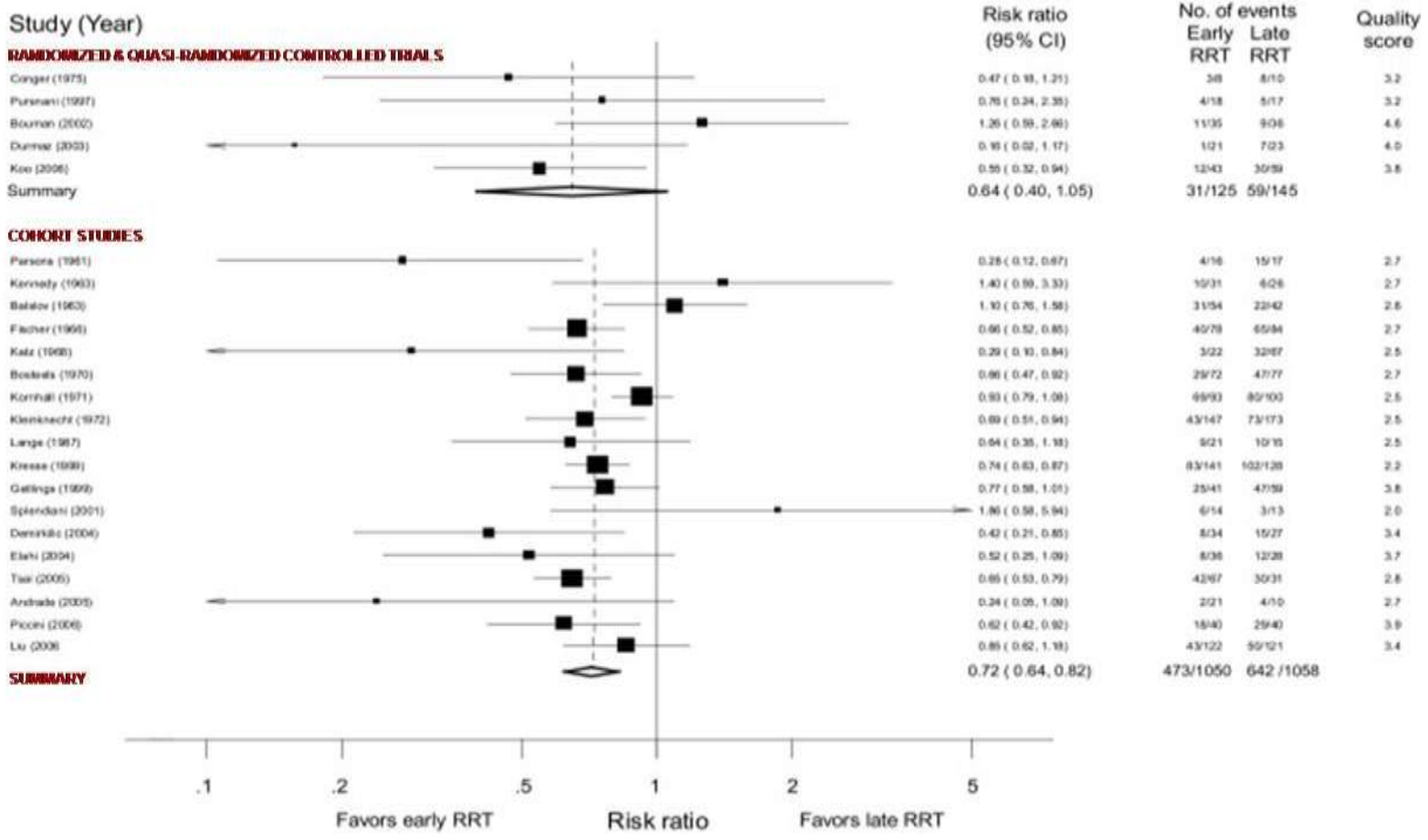
- Different doses of dialysis therapy
- **Definition of outcome**

Mortality

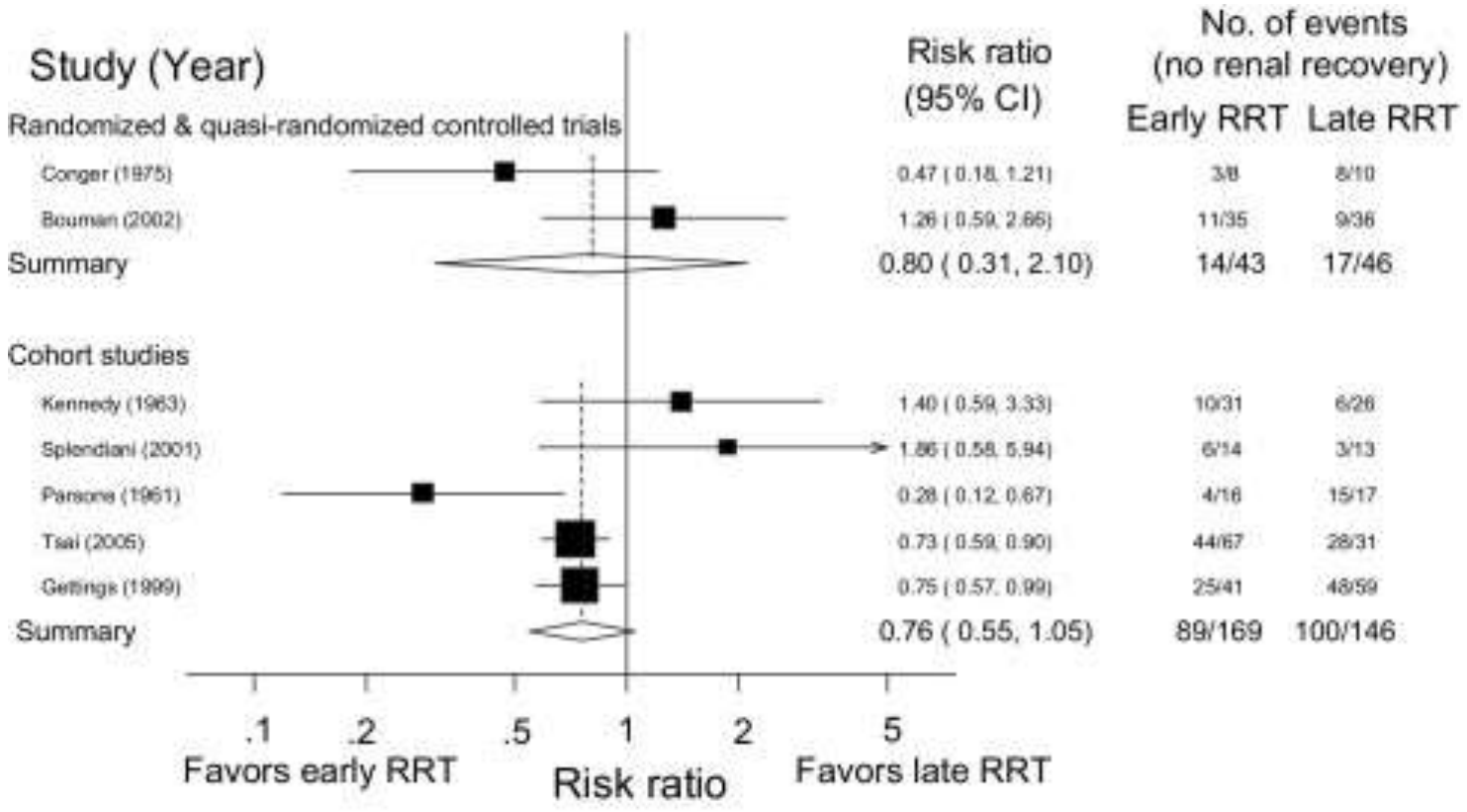
AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES
The Official Journal of
The National Kidney Foundation



V. Seabra et al, AJKD, 52: 272-284; 2008

AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES
The Official Journal of
The National Kidney Foundation

IMPACT ON RECOVERY RENAL FUNCTION

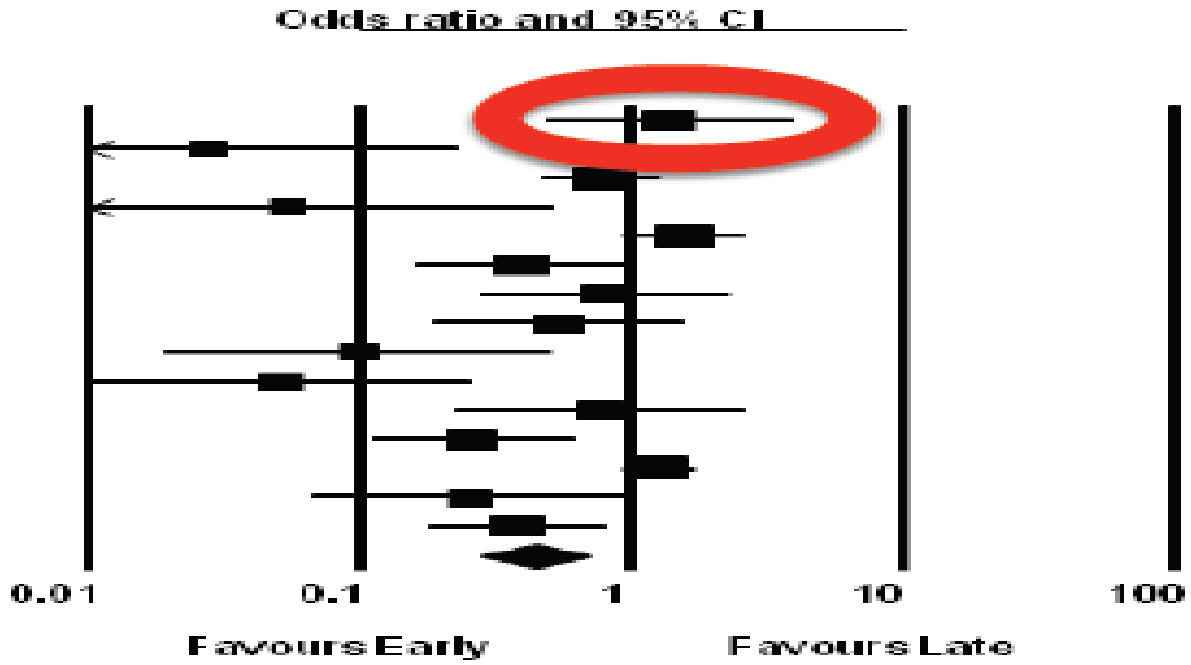


V. Seabra et al, AJKD, 52: 272-284; 2008

Journal of Critical Care

A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis

Constantine J Karvellas[1], Maha R Farhat[2], Imran Sajjad[3], Simon S Mogensen[4], Alexander A Leung[5], Ron Wald[6], Sean M Bagshaw[1*]



Critical care,2011

Standard Nomenclature for Renal Replacement Therapy in Acute Kidney Injury: Very Much Needed!

Claudio Ronco

Department of Nephrology, Dialysis and Transplantation, International Renal Research Institute of Vicenza (IRRIV), San Bortolo Hospital, Vicenza, Italy

Practice patterns in patients with acute kidney injury (AKI) requiring renal support or renal replacement are strongly affected by the results of trials whose value is often limited by a relatively small number of patients or an underpowered design. For this reason, registries and large databases are frequently used as a surrogate although database cleaning is often challenging or even impossible. All these barriers to a useful utilization of large

ADQI (Acute Dialysis Initiative) has traditionally led the field when it comes to changes in the treatment of AKI and continuous renal replacement therapies (CRRT), and also, in this case, a future consensus conference on the important contribution of information communication technology and large data management is in the planning phase. As a prerequisite for this consensus, the adoption of a common terminology would become quintessential.

December 2014

VOLUME 2 | ISSUE 1 | MARCH 2012
http://www.kidney-international.org

KDIGO Clinical Practice Guideline for Acute Kidney Injury

Section 5: Dialysis Interventions for Treatment of AKI

5.1.1: Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. (*Not Graded*)

5.1.2: Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single BUN and creatinine thresholds alone—when making the decision to start RRT. (*Not Graded*)

5.2.1: Discontinue RRT when it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care. (*Not Graded*)

5.2.2: We suggest not using diuretics to enhance kidney function recovery, or to reduce the duration or frequency of RRT. (*2B*)

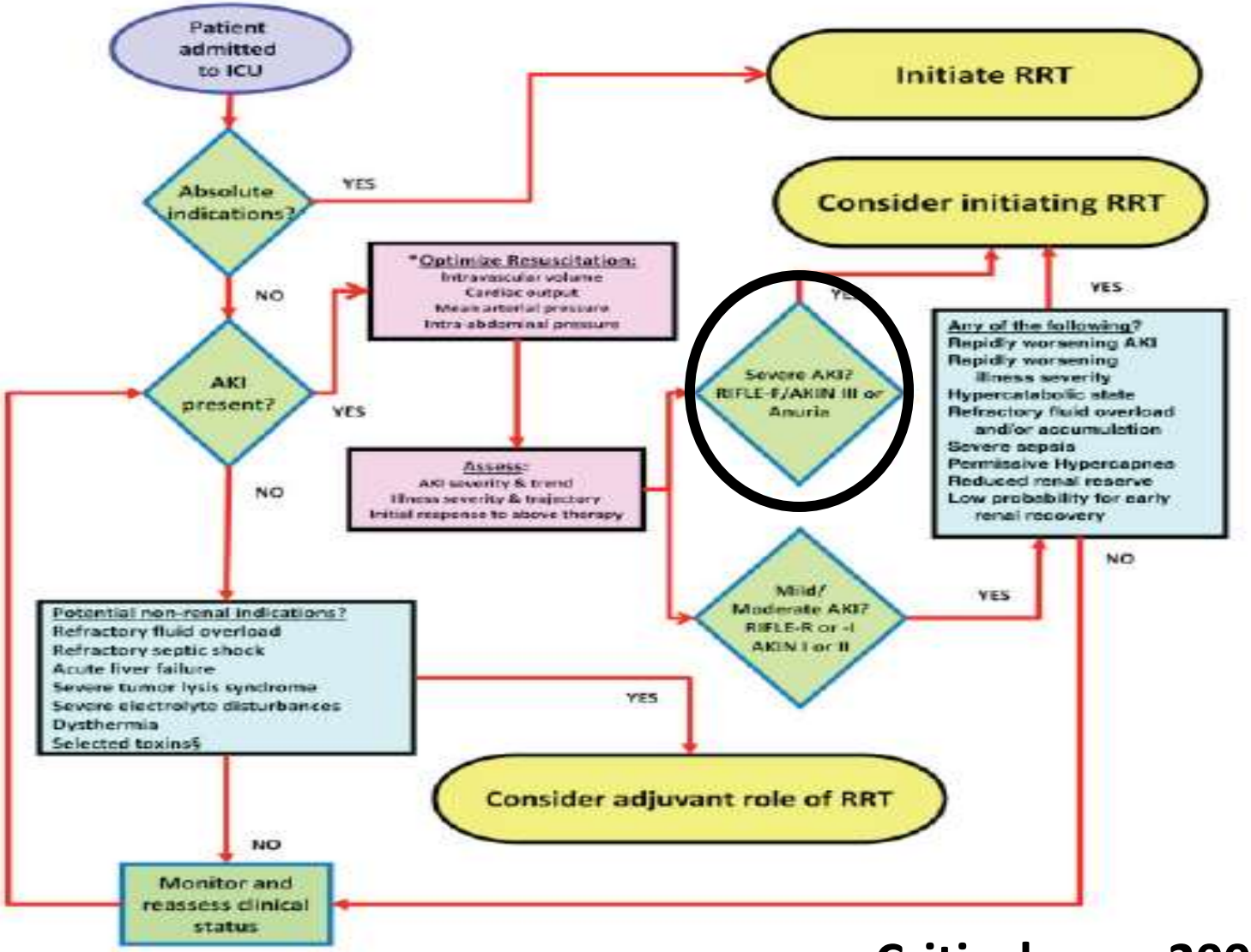
5.8.2: Provide RRT to achieve the goals of electrolyte, acid-base, solute, and fluid balance that will meet the patient's needs. (*Not Graded*)

5.8.3: We recommend delivering a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI. (*1A*)

5.8.4: We recommend delivering an effluent volume of 20–25 ml/kg/h for CRRT in AKI *(1A)*. This will usually require a higher prescription of effluent volume. (*Not Graded*)

A proposed algorithm for initiation of renal replacement therapy in adult critically ill patients

Sean M Bagshaw[1*], Dinna N Cruz[2*], RT Noel Gibney[1] and Claudio Ronco[2]

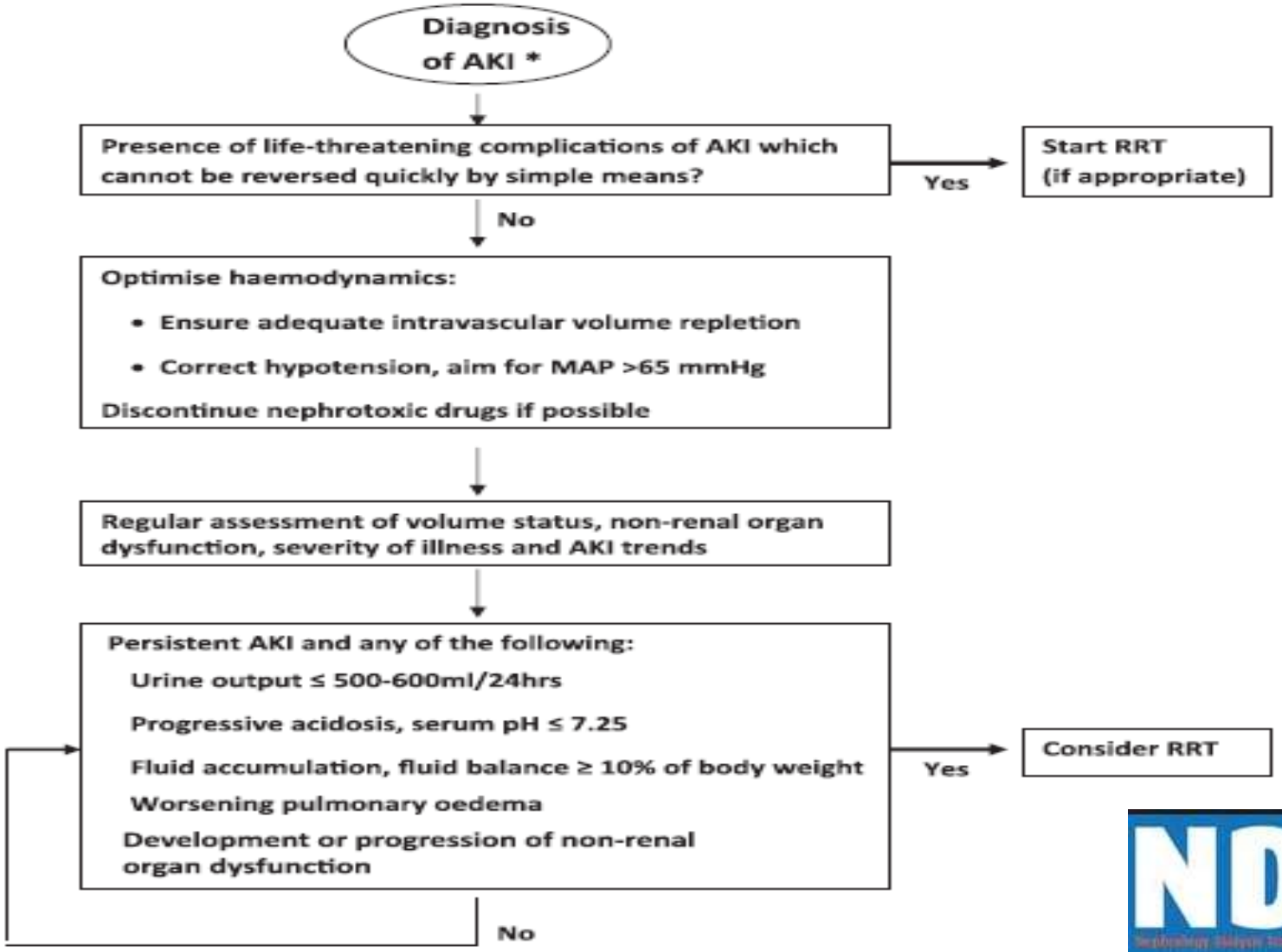


Critical care, 2009

Renal replacement therapy in critically ill patients with acute kidney injury—when to start

Nephrol Dial Transplant (2012) 27: 2242–2248

Marlies Ostermann, Helen Dickie and Nicholas A. Barrett



*Take home message

- Start in anticipation of Absolute Indications.
- Consider severity and likely course of patient's illness.
- Oliguria is better than biochemistry (500ml/d).
- Anticipate and avoid fluid overload with early RRT if necessary.
- You can use diuretics to modify *Fluid Balance but this* should not delay RRT .
- Can hold off if 'all is well'.


THANK
YOU